**IN THE CLAIMS**

Please substitute original pages 134-147 with new pages 134-147.

In claim 23, please delete the preamble phrase "The polynucleotide construct" and insert thereof -- A polynucleotide construct selected from the group consisting of --.

**IN THE DRAWINGS**

Please enter the attached "red-lined" corrections for Figures 13A-17, which show the corrected figure numbering for each respective figure.

## REMARKS

Claims 1-44 are pending in this application.

As suggested by the Examiner, original pages 134-147 are substituted with new pages 134-147, which provide better margin alignment as related to line numbering on the left hand side of the page.

The drawings and specification has been amended to correct an editorial oversight in regard to numbering of the attached drawings. First, original Figures 12A, 12 B, 13, 14, 15, and 16 have been renumbered 13A, 13B, 14, 15, 16 and 17, respectfully. In addition, in the Brief Description of the Drawings, at page 9, line 6 and line 12, the specification has been amended to accurately reflect the appropriate figure legend to the appropriate figure.

The specification has been amended to incorporate updated continuing data. Applicants thank the Examiner for pointing out this oversight to Applicants.

No new matter is added by entry of substitute pages of the original claims or correction of editorial oversights regarding the figures and figure legends.

Applicants presume that claim 24 is allowable, as this claim has not been identified as being subject to any of the rejections discussed *infra*.

### Rejection of Claim 23 Under 35 U.S.C. §112, Second Paragraph

Claim 23 stands rejected under §112, second paragraph as allegedly "being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." More specifically, it is allegedly unclear whether claim 23 recites a single construct or multiple constructs. Applicants overcome this rejection by amending the preamble to clearly recite multiple constructs, as specifically exemplified within this specification. Therefore, withdrawal of the rejection is proper and is requested. Claim 23 is now in proper form for allowance, as this claim has not been included in any additional rejection forwarded in the present Office Action.

**Rejection of Claims 1-5, 12-15 and 25 Under 35 U.S.C. §103(a)**

Claims 1-5, 12-15 and 25 stand rejected under 35 U.S.C. §103(a), as allegedly "being unpatentable over Almond et al (WO93/11250, published 10 June 1993) or Almond et al (GB 2 262 099A, May 12, 1991) in view of (Ulmer et al, Science Vol. 259, pages 1745-49, March 1993) and Woo et al (U.S. Patent 5,674,703, December 2, 1993)." More specifically, the Examiner takes the position that the primary reference of Almond et al (herein, "Almond") discloses a polynucleotide construction which induces the expression of at least two gene products, the use of such a construction as a vaccine, as well as expression of specific HIV antigens in a vaccine modality. The Examiner further takes the position that Ulmer et al (herein, "Ulmer") teaches "that polynucleotides can be introduced into cells essentially as "naked" or nonreplicating DNA, wherein the encoded proteins are expressed and act as an immunogen." Finally, the Examiner relies on the U.S. Patent No. 5,674,703 (herein, "Woo) to stand for the proposition of "a polynucleotide construction which induces the expression of a least two gene products." Applicants respectfully disagree, taking the position that these references, presented in their intended combination or any other combination, do not instill in the artisan of ordinary skill a reasonable expectation of success in practicing the claimed invention. This §103(a) rejection falls in view of the inherent weakness of Almond as a primary reference to support this §103(a) rejection. As noted above, the Examiner takes the position that Almond discloses not only bi-cistronic polynucleotide constructs, but also teaches the use of such a construct as an HIV vaccine, based solely on a 'wish list' of applications at page 6 of the PCT publication. However, the skilled artisan would not rely on mere statements such as these to either motivate, suggest or teach the invention as presently claimed. Instead, the skilled artisan would look to Almond in its entirety, not just the 'snapshot' relied upon by the Examiner. Almond teaches in Example 1 of the PCT publication the *in vitro* transfection of HELA cells with a plasmid construct encoding a poliovirus genome and a reporter gene, chloramphenicol acetyl-transferase (CAT). In Example 2, Almond purports to replace the CAT gene with an a DNA fragment encoding a rotovirus VP8 peptide. However, Almond cannot provide data showing expression of VP8, only that the DNA fragment still resides within the plasmid construct after *in vitro* passage through HELA cells. Therefore, Almond shows expression of a reporter gene in vitro, but not a more realistic antigen for use in a vaccination context. Needless to say, an inability to show expression of the gene of interest within an *in vitro* environment will hardly teach, suggest or motivate the artisan of ordinary skill in the art to use Almond as the primary teaching to combine with Ulmer and Woo to then somehow arrive at the invention as presently claimed, an invention based on the *in vivo* delivery and expression of the antigen of interest.

The weakness of Almond is exacerbated by the application of Ulmer to this present §103(a) rejection. The Examiner takes the position that Ulmer teaches "that polynucleotides can be introduced into cells essentially as "naked" or nonreplicating DNA, wherein the encoded proteins are expressed and act as an immunogen." In other words, the Examiner has taken the position that a single disclosure of a DNA polynucleotide which promotes protective host immunity against challenge from one specific microorganism teaches that all polynucleotides expressing a viral or bacterial antigen will be useful for the purpose of providing protective immunity against any other of hundreds of microorganisms. Applicants respectfully disagree and take the position that Ulmer stands for what it discloses: a DNA vaccine encoding a single influenza nucleoprotein antigen within a host to provide protection against a challenge by influenza. Therefore, Applicants respectfully take the position that Ulmer, alone or in the intended combination with Almond and Woo, offers nothing to the skilled artisan that would instill a reasonable expectation of success in using the polynucleotide constructs of the present invention: bi- or tri-cistronic DNA polynucleotide vaccines providing for coordinated *in vivo* expression so as to provide humoral and cellular mediated immunity against a specific viral or bacterial challenge.

Finally, Woo describes a viral, replicative system based on a papillomavirus genome which is supposedly useful for long term expression in the liver. Applicants respectfully take the position that this is the type of gene therapy vector which Applicants are avoiding by utilizing vaccine constructions as disclosed in the present specification. The disclosure of a replicating-based viral system based on a pappilomavirus system does nothing, even in the intended combination with Almond and Ulmer, to teach, suggest or motivate the artisan the presently claimed invention. It should be noted that the bi-cistronic nature of the Woo constructs (i.e., E1 and E2 expression) do not express a gene therapy or vaccination-based protein, but instead are expressed for the sole purpose of promoting replication of the papillomavirus-type vector. It should be noted that Woo gives no guidance to expression prophylactic or therapeutic levels of a transgene or vaccine antigen, instead relying on 'paper' examples in Example 7 and Example 8. There is little to Woo other than a description of a complicated, viral-based system that expresses two papillomavirus proteins to provide for required proteins *in trans* to support replication of these viral-based vectors.

At best the claimed invention as a whole, in view of the cited references, would be "obvious to try." However, it is well settled that the "obvious to try" standard is an improper standard for which to base a *prima facie* case of obviousness. *In re O'Farrell*, 7 USPQ2d 1673, 1681 (Fed Cir 1988). The CAFC in *O'Farrell* stated that one question to be asked is: "when is an invention that was obvious to try, nevertheless nonobvious?" Id at 1680-1681. One such area the *O'Farrell* court noted was a situation "where the prior art gave only

general guidance as to the particular form of the claimed invention or how to achieve it. Id at 1681, citing *In re Dow Chemical Co.* 5 USPQ 1529, 1532 (Fed Cir 1988); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.* 231 USPQ 81, 90-91 (Fed Cir 1986), cert. denied 107 S.Ct. 1606, 94 L.Ed.2d 792(1987); *In re Tomlinson*, 150 USPQ 623, 626 (CCPA 1966). The CAFC concluded that the proper standard is "a reasonable expectation of success." In conclusion, Almond instills no such expectation, or any motivation to look elsewhere (such as Ulmer and/or Woo) to support the present claims. The defects of Almond would send the skilled artisan away from the present invention, not toward the additional teachings of Ulmer and Woo. The combination of the references as forwarded by the Examiner does nothing to increase their worth in any attempt to put forth a *prima facie* case of obviousness. Neither Almond, Ulmer or Woo, in any way, shape or form, supports an obviousness rejection to the present claims. Therefore, even if the "obvious to try" tag is appropriate, the claimed invention is nonobvious in light of the deficiencies of these three references teach or suggest the claimed invention. Therefore, Applicants respectfully request that this §103 be withdrawn.

**Rejection of Claims 6-11, 16-22, 35, 39-42 and 44 Under 35 U.S.C. §103(a)**

Claims 6-11, 16-22, 35, 39-42 and 44 stand rejected under 35 U.S.C. §103(a), as allegedly "being unpatentable over Almond et al (WO93/11250, published 10 June 1993) or Almond et al (GB 2 262 099A, May 12, 1991) in view of (Ulmer et al, Science Vol. 259, pages 1745-49, March 1993) and Woo et al (U.S. Patent 5,674,703, December 2, 1993) as applied to claims 1-5, 12-15 and 25, and further in view of Schwartz et al (Schwartz et al, Virology, Vol. 183, pages 677-686, 1991) or Smarda et al (Gene Vol. 137, pages 145-149, 1993)." Applicants respectfully disagree and rely on the discussion provided *supra* in regard to Almond, Ulmer and Woo to overcome the basis of the present rejection. Again, despite any teachings from Schwartz and Smarda, such teachings are rendered moot in view of reliance upon the teachings of Almond, Ulmer and Woo "as applied to claims 1-5, 12-15 and 25." Therefore, Applicants respectfully take the position that this §103(a) rejection is overcome in view of the discussion *supra* regarding Almond, Ulmer and Woo, rendering an analysis of Schwartz and/or Smarda irrelevant. To this end, Applicants respectfully request that this §103(a) rejection be withdrawn.

**Rejection of Claims 26-34, 36-38 and 43 Under 35 U.S.C. §112, First Paragraph**

Claims 26-34, 36-38 and 43 stand rejected under 35 U.S.C. §112, first paragraph, allegedly "as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly

connected, to make and/or use the invention," Applicants respectfully disagree and reiterate earlier correspondence with the PTO that this rejection is nothing more than an 'old style' §101 utility rejection clothed in a §112, 1¶ rejection. The Examiner relies on a 1993 review article by Haynes to stand for the proposition the HIV field is muddled, presumably due to questions surrounding the relevance of immunological data generated from non-human primates when compared to a potential human response. This is a utility issue, not an enablement issue. Applicants exemplify numerous bi- and tri-cistronic constructs which enable one of ordinary skill in the art to test further in the organism of choice, whether it be a non-human primate model or in human clinical trials. In other words, support for the proposition of using these bi- and tri-cistronic to generated an appropriate immune response, in particular in the area of HIV, is shown throughout the specification. Applicants guide the artisan step by step: through construction of specific DNA polynucleotide vaccines (e.g., Example 3, part I), confirmation that a multi-cistronic construct is expressed *in vitro* (e.g., Example 3, part II) and the generation of appropriate antibodies subsequent vaccination of a non-human primates, rhesus and African Green monkeys (e.g., Example 3, part III and the table on page 55 and the table on page 56), and appropriate CTL responses (e.g., Example 16 and Figure 16). Therefore, Applicants respectfully take the position that the instant specification discloses novel and nonobvious bi- and tri-cistronic polynucleotides and related methods which are useful in eliciting immune responses *in vivo*. It is fully within the grasp of the artisan of ordinary skill to test further the vaccines of the present invention.
No experimentation is necessary, only trials within the target host to test the vaccine constructs of the present invention. Therefore, as noted *supra*, Applicants respectfully take the position that the Examiner's position is not appropriate and does nothing more than mask this old school §101 utility rejection under the guise of an enablement rejection. This rejection suggests that nothing short of FDA approval subsequent to human clinical trials would be necessary to provide an enabling specification for methodology associated with products useful as DNA vaccines. This position stands for nothing more than the antiquated §101 rejection which would state that an invention is not useful until it has been tested in the target host, namely a human. It is well settled by the Patent Office that such a high standard to determine utility is not appropriate for any invention, including biotechnology inventions. Applicants take the position that mere transfer of this position to a different statutory rejection is not appropriate. To this end, Applicants take the position that such a rejection is improper and should be withdrawn as applied to method claims 26-34, 36-38 and 43. Withdrawal of the rejection is proper and is hereby requested.

The Examiner is invited to contact the undersigned attorney if clarification is required on any aspect of this response, or if any of the claims are considered to require further amendment to be placed in condition for allowance after entry of this Amendment.

Respectfully submitted,

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